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EXAMINER	
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ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/057,150	CLARY, DOUGLAS	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *04 January 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8,10,11,16-18 and 20-29* is/are pending in the application.

4a) Of the above claim(s) *1,6-8,10,11,16-18 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 1/4/2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/057,150 is acceptable and a CPA has been established. An action on the CPA follows.

Preliminary Amendment

2. Preliminary Amendment filed 1/14/02 has been entered.

Response to Applicants arguments under *35 USC § 101*

The following is a quotation of 35 U.S.C. 101:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 23-29 rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claim 24 remains rejected under 35 USC § 101, for reasons of record (1/13/2002) and also for the reasons given below. Amended claims 23, 25 and 26 remain rejected under 35 USC § 101, for reasons of record (1/13/2002) and also for the

reasons given below. New claims, 27-29 are rejected under 35 USC § 101, for the reasons given below.

Applicants traverse the claim rejection under 35 USC § 101. Applicant asserts there is a well established utility for the claimed invention. Applicants argue:

a) Proto-oncogenes are prefixed with a 'c'. Therefore, C-RET is a proto-oncogene. Several human diseases are linked to mutations in the RET proto-oncogene. Further, since mutations in the RET proto-oncogene have been linked to several human diseases, the claimed method of identifying compounds that modulate the function of C-RET receptor protein kinase possesses a specific and substantial utility.

b) Durbec et al studied many aspects of the interaction between RET and GDNF, including the effect on neuronal response and concluded that their data "strongly suggests that the C-RET locus encodes a functional receptor for GDNF. Buj-Bello showed that GDNF promotes neuronal survival by signaling through a multi-component receptor that consists of RET and a member of a GPI-linked family of receptors that determine ligand specificity.

c) Takahashi discloses certain diseases (Hirschsprungs's disease, MEN2A, MEN2B, and papillary thyroid carcinoma) are caused by RET mutations

Applicants arguments have been fully considered but not found persuasive and are addressed below.

Examiner agrees the C-RET is the proto-oncogene. The specification discloses the **C-RET is an "orphan receptor"** (page 16, lines 11-16). The specification further discloses, "It is called an orphan receptor because no ligand has been identified which

directly activates it" (page 16, 20-21). The specification further states, "In addition, the **term "orphan receptor" as used herein refers to an RPTK without a known function"**, see page 16, lines 21-23. The specification clearly states that C-RET is an orphan receptor without a known function. Neither, Applicant's specification or prior art show the that expressing C-RET in cells, contacting said cells with a peptide of less than 20 amino acids, a non-peptide organic molecule or an antibody has an effect on any of the phenotypes as claimed by Applicant.

The role of C-RET in cellular function is not known. Although, Durbec studied the interaction between RET and GDNF, their suggestion that the C-RET locus encodes a functional receptor for GDNF was based on phosphorylation and binding studies on RET (mutated form of C-RET) and not on C-RET. Further, as discussed below, C-RET is not the receptor of GDNF. Durbec also discloses the *in vivo* function of GDNF is at present unknown (page 789, column 2, last paragraph). Therefore, if the function of GDNF is unknown and the function of C-RET is also unknown, what is the use for compounds identified by claimed method, except for further research. The claimed method itself is a tool for studying the function of an orphan receptor, which does not have utility under 35 USC § 101.

Buj-Bello showed that GDNF promotes neuronal survival by signaling through a multi-component receptor that consists of RET and a member of a GPI-linked family of receptors that determine ligand specificity. The specific receptor for C-RET was not disclosed or known. Just because GDNF promotes neuronal survival by signaling through a multi-component receptor that consists of RET does not provide utility for C-

RET. Buj-Bello did not show that GDNF promotes neuronal survival, by signaling through a C-RET nor did they disclose the member of a GPI-linked family of receptors that determine ligand specificity for C-RET. Therefore, if the function of GDNF is unknown and the function of C-RET is also unknown, what is the use for compounds identified by claimed method, except for further research. Even if a compound identified by claimed method phosphorylates C-RET what would be the use of said compound? Phosphorylation of C-RET has not been shown to produce a physiological function that would confer utility on the claimed invention. C-RET and RET have not been shown to have similar functions. Compounds identified by instant method would not be expected to have the same effect, or any effect on RET because the mutated protein is shown to be structurally and functionally different to the protooncogene. For example, in Hirschsprung's disease (HSCR), RET protein lacks a kinase domain. Other mutations cause constitutive activation of the kinase function of RET. Fox (U. S. Patent 6,455,277, Ref A, claims priority to May 9, 1996, Patent date September 24, 2002) discuses the reference of Tsuzuki. The exact role of C-RET in the development or function of central/ peripheral nervous systems, in the excretory central/ peripheral nervous systems and in the excretory system of the mouse embryo was not disclosed (column 53). Further, Fox states, "A functional ligand of RET receptor has not been identified, thereby limiting a further understanding of the molecular mechanism of RET signaling. Mutations in the C-RET gene are associated with inherited preposition to cancer in familial medullary thyroid carcinoma (FMTC) and multiple endocrine neoplasia type 2A (MEN2A) and 2B (MEN 2B). These diseases are probably caused by "gain of

function" mutations that constitutively activate the RET kinase". Also stated, "Another ret-associated genetic disorder Hirschsprung's disease (HSCR), is characterized by congenital absence of parasymphetic innervations in the lower intestinal tract". The most likely causes of HSCR are disclosed to be nonsense mutations that result in the production of truncated RET protein lacking a kinase domain or missense mutations that inactivate the RET kinase. How C-RET and GDNF interact and the physiological effect of said interaction is not disclosed in the specification or in the prior art references supplied by Applicant Fox discloses GDNFR (receptor for GDNF) may be used to mediate the autophosphorylation of RET on the 170 Kd mature form of the protein but not on the 150KD precursor form (column 55). The effect of GDNF on RET is disclosed to be cell specific and dependent on a specific GDNFR. Cells lacking GDNFR were not able to mediate the effect of GDNF on RET (see discussion, especially column 58). Instant specification does not disclose the mechanism of C-RET and RET action or the additional proteins (specific GDNF receptor) that are required to form the basis of a functional assay, which may signal through the pathway that is most likely to involve C-RET or RET action. Again, without knowledge of how C-RET functions, the compounds identified by claimed method may have phenotypic effects completely unrelated to those caused C-RET or RET.

The claimed method does not require cells to be responsive to GDNF, more specifically the claims have been constructed sothat they do not read on assaying GDNF action. Ibanez (US Patent 6,696,259, Ref B, priority date June 27, 1996, patent date February 2004) discloses the several isoforms of C-RET mRNA have been

described, but their biological role is not known. Further, in several cell lines C-RET may be of different molecular weights (160 kD, 140kD, 120, kD) (column 8). Increase in tyrosine phosphorylation of 190kD C-RET and of a 170 kD form was also observed (column 30). Ibanez disclose the effect of GDNF on RET is also cell specific and requires a specific GDNF receptor to form a complex that will form part of the signaling pathway. The GDNF receptor is identified and it is not C-RET. Therefore, based on the Ibanez Patent, it is even harder to postulate what effect a compound identified by claimed method would have on the RET based on the different C-RETs that may be phosphorylated in a cell.

Klein (US Patent 6,504,007, Ref C, priority date March 1996, patent date January, 2003) disclose the effect of GDNF on RET is cell specific and requires a GDNFR receptor to form a complex that will form part of the signaling pathway. Klein discloses GDNF-induced tyrosine autophosphorylation of RET depends on GDNFRalpha (column 6 and 69).

The patents of Fox, Ibanez, and Klein disclose many aspects of RET signaling that were not disclosed in instant specification, or in the prior art. Although GDNF may promote tyrosine phosphorylation of C-RET there is no showing of what specific role the phosphorylated/non phosphorylated C-RET plays in survival of enteric, sympathetic and sensory neurons. Applicant's assertion that GDNF binds RET does not give it utility. Further, there is no showing that any compounds identified by claimed method promote the survival and phenotype of central dopaminergic, noradrenergic and motor neurons via its interaction with for C-RET. Further claimed method does not even

require the cells to be responsive to GDNF, and therefore signal through the mechanism disclosed by Fox, Ibanez, and Klein. The specification nor prior art discloses that compounds identified by claimed method promotes the survival and phenotype of cells. There is no showing of what is the specific biological pathway governing C-RET action and how it is specifically involved in cell survival or production of a particular phenotype. There is no showing of what specific cancers result as a consequence of over/under expression of C-RET. No compounds are disclosed that inhibit C-RET function. No compounds/ pharmaceutical agent disclosed that can be used as possible anti-cancer agents or inhibitors of RET dysfunction.. The utilities of instant invention are specific only when the function of C-RET is known, and then they can be important for designing compounds that will prevent or treat known diseased involved in C-RET dysfunction. Applicant does not provide any data showing that modulating C-RET function can treat a specific disease. Further, although, compounds may have an effect on C-RET to induce tyrosine phosphorylation, there is a no real world use for identifying such compounds without knowing the specific function of C-RET. If a compound does in fact phosphorylate C-RET, what is the use of that compound? Further research has to be done on the compound to assign a utility.

The utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the claimed method for identifying compounds that modulate C-RET function. Applicant argues C-RET, is said to have a potential function based upon its phosphorylation by GDNF and its relationship to RET. After further research, a specific and substantial

credible utility might be found for the claimed method of using C-RET. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are useful to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of useful as it appears in 35 U.S.C. 101, which requires that an invention must have either an immediately apparent or fully disclosed real world utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

Claims of instant invention are drawn to a method of using C-RET, a protein of undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the C-RET used in the method of the instant application was, as of the filing date, useful for "diagnosis, prevention and treatment of disease", such as cancers etc. Until some actual and specific significance

can be attributed to C-RET, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or real world utility as of the filing date.

C-RET may share some structural similarity to other orphan RPTKs disclosed on page 16 of the specification. Some of the other orphan RPTKs may be phosphorylated by GDNF, but the phosphorylation of an orphan RPTKs does not disclose its biological function. GDNF may not even be the natural ligand for C-RET. In the absence of knowledge of the biological significance of C-RET, there is no immediately evident patentable use for the methods of instant invention. To employ C-RET of the instant invention in any of the disclosed methods would clearly be using it as the object of further research. Such a use has been determined by the courts to be a utility, which, alone, does not support patentability. Since the instant specification does not disclose a real world use for C-RET, then the claimed invention as disclosed does not meet the requirements of 35 U.S.C. 101 as being useful.

In conclusion, the utilities asserted by Applicant are not specific or substantial. Since no specific function of C-RET is known, and the hypothesized function is based entirely on conjecture, the asserted utilities are not specific to C-RET, but rather are based on its ability to be phosphorylated by GDNF. Neither the specification nor the art of record disclose physiological function of C-RET or phosphorylated C-RET. Similarly, neither the specification nor the art of record disclose any instances where disorders can be effected by interfering with the activity using C-RET. Thus the corresponding asserted utilities are essentially using C-RET in methods to identify compounds that

may be used to affect disease states associated with C-RET , or as targets for drug discovery. Therefore the asserted utilities are essentially methods of testing for or for potentially treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating or testing for compounds that interact with C-RET which may be implicated in an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for C-RET or methods of instant invention, further experimentation is necessary to attribute a utility to C-RET and methods of its use. See Brenner v. Manson, 383 U.S. 519, 535□36, 148 USPQ 689, 696 (1966) (noting that Congress intended that no patent be granted on a chemical compound whose sole utility consists of its potential role as an object of use-testing, and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."). Therefore, since C-RET is an orphan receptor and not supported by either a specific and substantial asserted utility or a well established utility, it follows that the methods of using C-RET are also not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above.

Response to Applicants arguments under *35 USC § 112, 1st paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 23-29 also rejected under 35 U.S.C. 112, first paragraph. Claim 24 remains rejected under 35 U.S.C. 112, first paragraph, for reasons of record (1/13/2002) and also for the reasons given above. Amended claims 23, 25 and 26 remain rejected under rejected under 35 U.S.C. 112, first paragraph, for reasons of record (1/13/2002) and also for the reasons given above. New claims, 27-29 are rejected under rejected under 35 U.S.C. 112, first paragraph, for the reasons given above.

Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant argues the invention is supported by both a specific and substantial asserted utility and a well established utility, for the reasons set forth in their arguments under 35 U.S.C 101, a person of skill in the art would know how to use the claimed invention. Withdrawal of the rejection is requested. Applicant's arguments have been fully considered but not found persuasive. Even if Applicant overcomes the rejection rejected under 35 U.S.C. 101/112, first paragraph (disclosed above), claims 23-29 would also be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The essential features required to practice the claimed method are not disclosed in the claims. Further the claims as written do not specifically identify one or more compounds that modulate the function of C-RET receptor protein kinase. Further, dependent claims require the use of natural binding partner, which was unknown to Applicant. Certain phosphorylated products are also required to practice the method, these were also unknown to the Applicant. Further the method cannot be practiced in cells lacking GDNG receptor, also unknown to Applicant.

The method is directed to identifying one or more compounds that modulate the function of C-RET. The goal of the method is achieved by either, a) contacting cells expressing C-RET with one or more compounds and comparing a phenotype of said cells to a phenotype of cells not expressing said C-RET receptor protein, **or,** b) contacting cells expressing C-RET with one or more compounds and comparing a phenotype of said cells to a phenotype of cells expressing C-RET receptor protein, Comparing the phenotype of cells expressing C-RET contacted with compounds to the phenotype of cells that do not express said C-RET receptor protein would not necessarily identify the compounds as a modulator of the function of C-RET receptor protein kinase for reasons given below. The effect on phenotype may be due to the action of compounds on the function of a protein unrelated to C-RET. For example, if the function measured is the phenotype of cell size, cells expressing C-RET may have a cell size X, cells not expressing C-RET may have a cell size Y. Contacting compounds with cells expressing C-RET may change the cell size to Z. Therefore comparing cell sizes Y and Z does not support the conclusion of identifying compounds as modulators

of C-RET function. Further, if the phenotype measured is phosphorylation of C-RET, said phenotype cannot be measured in cells lacking C-RET, therefore a comparison cannot be made as required in step (c) of the claim. Also, comparing the phenotype of cells expressing C-RET, contacted with compounds, to the phenotype of cells expressing C-RET receptor protein, but not contacted with said compound, would not necessarily identify the compounds as a modulator of the function of C-RET receptor protein for reasons given below. The effect on phenotype may be due to the action of compounds on the function of a protein unrelated to C-RET. For example, if the function measured is the phenotype of cell size, cells expressing C-RET and contacted with compound may have a cell size U, cells expressing C-RET and not contacted with compound may have a cell size V. Therefore comparing cell sizes U and V does not support the conclusion of identifying a compound as modulator of C-RET function. Further, if the phenotype measured is cell proliferation, incubating a cell expressing C-RET in the presence or absence of compound does not directly identify the compounds as a modulator of the function of C-RET receptor protein kinase. Thousands of other proteins may be affected by compounds that regulate cell proliferation. Further, the method as claimed, cannot identify more than one compound without the appropriate controls. For example, if a hundred compounds are added to the assay there is no step that differentiates which of said compounds actually modulates function. Therefore the method lacks essential steps that are required to practice the invention as claimed.

The specification discloses the C-RET is an "orphan receptor" (page 16, lines 11-16). The specification further discloses, "It is called an orphan receptor because no

ligand has been identified which directly activates it" (page 16, 20-21). Since the specification does not disclose any ligands that bind C-RET, the natural binding partner is not known. Therefore, the natural binding partner of C-RET that is a protein comprising SH2 domains, a protein comprising SH3 domains, guanine nucleotide exchange factor, a protein phosphatase and protein kinase is also not known. Further, since the natural binding partner is not known, the interaction of C-RET receptor protein with natural binding partner cannot be determined. Also, since the natural binding partner and the signaling pathway of C-RET is not known, the phosphorylated product of the protein kinase catalytic activity of C-RET is also not known.

Neither, Applicant's specification or prior art show that expressing C-RET in cells, contacting said cells with a peptide of less than 20 amino acids, a non-peptide organic molecule or an antibody has an effect on cell size, cell shape, cell proliferation, cell survival, cell death or utilization of a metabolic nutrient.

The complexity of C-RET interaction is disclosed by Fox, Ibanez, and Klein (discussed above).

The role of C-RET in cellular function is not known. The specific receptor for C-RET is not disclosed or known. Fox discloses thata functional ligand of RET receptor has not been identified, thereby limiting a further understanding of the molecular mechanism of RET signaling. Mutations in the C-RET gene are associated with certain diseases. These diseases are probably caused by a) "gain of function" mutations that constitutively activate the RET kinase, b) mutations that result in the production of truncated RET protein lacking a kinase domain , c) missense mutations that inactivate

the RET kinase. How C-RET and GDNF interact and the physiological effect of said interaction are not disclosed in the specification or in the prior art references supplied by Applicant Fox discloses GDNFR (receptor for GDNF) may be used to mediate the autophosphorylation of RET on the 170 Kd mature form of the protein but not on the 150KD precursor form (column 55). Ibanez discloses the several isoforms of C-RET mRNA have been described, but their biological role is not known. Further, in several cell lines C-RET may be of different molecular weights (160 kD, 140kD, 120, kD) (column 8). Increase in tyrosine phosphorylation of 190kD C-RET and of a 170 kD form was also observed (column 30).

Claimed method does not require cells to be responsive to GDNF, more specifically the claims have been constructed so that they do not read on assaying GDNF action. Fox, Ibanez, and Klein all disclose for C-RET to signal its effect (in instant case produce a particular phenotype) the cell must be responsive to GDNF. All cells are not responsive to GDNF. Fox discloses the effect of GDNF on RET is cell specific and dependent on a specific GDNFR. Cells lacking GDNFR were not able to mediate the effect of GDNF on RET. Instant specifcation does not disclose the mechanism of C-RET and RET action. Also, additional proteins (specific GDNF receptor) that are required to form the basis of a functional assay, which may signal through the pathway that is most likely to involve C-RET or RET action are also not disclosed. Ibanez discloses thatthe effect of GDNF on RET is also cell specifc and requires a specifc GDNF receptor to form a complex that will form part of the signaling pathway. The GDNF receptor is identified and it is not C-RET, it is a molecule that can

form a complex with C-RET. Klein discloses that the effect of GDNF on RET is cell specifc and requires a GDNFR receptor to form a complex that will form part of the signaling pathway. Klein discloses GDNF-induced tyrosine autophosphorylation of RET depends on GDNFRalpha. Therefore, based on the teachings of Fox, Ibanez, and Klein, randomly expressing C-RET in cells will not result in a predictable phenotype. It is even harder to predict which C-RET will be a functional kinase responsible for the phenotypes claimed, based on the various phosphorylated products. Again, without knowledge of how C-RET functions, the compounds identified by claimed method may have phenotypic effects completely unrelated to those caused C-RET or RET. Applicant has not disclosed how to use said compounds.

The patents of Fox, Ibanez, and Klein disclose many aspects of RET signaling that were not disclosed in instant specifcation, or in the prior art. Although GDNF may promote tyrosine phosphorylation of C-RET, there is no showing of what specific role the phosphorylated/non phosphorylated C-RET plays in survival of enteric, sympathetic and sensory neurons. Therefore, it cannot be predicted if contacting cells will cause an effect on cell shape, cell size, cell proliferation, cell differentiation, cell survival or utilization of metabolic nutrients. Further, there is no showing that any compounds identified by the claimed method effects the phenotype of cell shape, cell size, cell proliferation, cell differentiation, cell survival or utilization of metabolic nutrients. The change in the utilization of a particular nutrient as result of theC-RET signaling is not disclosed. Further, the claimed method does not even require the cells to be responsive to GDNF, and therefore signal through the mechanism disclosed by Fox,

Ibanez, and Klein. Other mechanisms, using cells not responsive to GDNF, are not disclosed. The specification nor prior art discloses any compounds identified by theclaimed method that promote changes in cell shape, cell size, cell proliferation, cell differentiation, cell survival or utilization of metabolic nutrients. There is no showing of what is the specific biological pathway governing C-RET action and how it is specifically involved in cell survival or production of a particular phenotype. No compounds are disclosed that specifically inhibit C-RET function.

While the person of ordinary skill in the art would, in light of the specification be able to express a C-RET in a cell, the scope of the claims, which encompass contacting any cell (including cells not responsive to GDNF) expressing a C-RET, with a compound and measuring any phenotype to monitor the function of C-RET receptor protein kinase, are not enabled by the disclosure. The disclosure does not teach thatmodulation of C-RET will have any specifc effects cell shape, cell size, cell proliferation, cell differentiation, cell survival or utilization of metabolic nutrients. The effect on natural binding partner of C-RET or the phosphorylated product of C-RET is not disclosed. The natural binding partner of C-RET or the phosphorylated product of C-RET is not disclosed. The critical requirement that the cells be responsive to GDNF is not disclosed. Therefore due to the large quantity of experimentation necessary to produce a functional assay that would fulfill the goals of claim 23 with the method steps claimed, taking into consideration unpredictability of identifying a ligand partner of C-RET or phosphorylated product produced by C-RET, and the breadth of the claim which fails to recite a specifc kinase activity, ligand partner of C-RET and phosphorylated product

produced by C-RET functional limitations, undue experimentation would be required of the skilled artisan to make or use the claimed invention as claimed.

New Rejections

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 23-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23 is indefinite because it is not clear if C-RET receptor protein kinase, C-RET receptor protein and RET are the same compound. In the preamble of the claim, it is not clear if the function modulated is kinase activity of C-RET or some other C-RET protein function. The claim is also rejected for the reasons given below. The method is directed to identifying modulation of function of C-RET receptor protein kinase, the cells in (a) express C-RET receptor protein and the conclusion is that modulators of C-RET function are identified. Further, claim 23 is indefinite because the method steps do not achieve the goal of identifying one or more compounds that modulates the function of C-RET receptor protein kinase as stated in the preamble. An acceptable method claim must contain three sections: 1) a preamble, 2) method steps that clearly define what is to be done in each step, and 3) a conclusion that what was stated in the preamble was

achieved. The method is directed to identifying one or more compounds that modulate the function of C-RET. The goal of the method is achieved by either, a) contacting cells expressing C-RET with one or more compounds and comparing a phenotype of said cells to a phenotype of cells not expressing said C-RET receptor protein, **or,** b) contacting cells expressing C-RET with one or more compounds and comparing a phenotype of said cells to a phenotype of cells expressing C-RET receptor protein, Comparing the phenotype of cells expressing C-RET contacted with compounds to the phenotype of cells that do not express said C-RET receptor protein would not necessarily identify the compounds as a modulator of the function of C-RET receptor protein kinase for reasons given below. The effect on phenotype may be due to the action of compounds on the function of a protein unrelated to C-RET. For example, if the function measured is the phenotype of cell size, cells expressing C-RET may have a cell size X, cells not expressing C-RET may have a cell size Y. Contacting compounds with cells expressing C-RET may change the cell size to Z. Therefore comparing cell sizes Y and Z does not support the conclusion of identifying a compound as modulator of C-RET function. Further, if the phenotype measured is phosphorylation of C-RET, said phenotype cannot be measured in cells lacking C-RET, therefore a comparison cannot be made as required in step c of the claim. Also, comparing the phenotype of cells expressing C-RET, contacted with compounds, to the phenotype of cells expressing C-RET receptor protein, but not contacted with said compound, would not necessarily identify the compounds as modulators of the function of C-RET receptor protein for reasons given below. The effect on phenotype may be due to the action of

compounds on the function of a protein unrelated to C-RET. For example, if the function measured is the phenotype of cell size, cells expressing C-RET and contacted with compound may have a cell size U, cells expressing C-RET and not contacted with compound may have a cell size V. Therefore comparing cell sizes U and V does not support the conclusion of identifying a compound as modulator of C-RET function. Further, if the phenotype measured is cell proliferation, incubating a cell expressing C-RET in the presence or absence of compound does not directly identify the compounds as a modulator of the function of C-RET receptor protein kinase. Thousands of other proteins may be affected by compounds that regulate cell proliferation. Further it is not clear how more than one compound can be shown to modulate C-RET receptor protein kinase without the appropriate controls. For example, if a hundred compounds are added to the assay there is no step that differentiates which of said compounds actually modulates function. Therefore the method lacks essential steps that are required to practice the invention as claimed. Also the claim is indefinite because it is not clear what is included or excluded by the term "phenotype". The specification, on page 13, states, and "The term cell phenotype" refers to the outward appearance of a cell or tissue or the function of a cell or tissue". The functions of the cell or tissue that comprise the term "phenotype" are not disclosed. The art accepted meaning of phenotype is, 'the visible properties of an organism that are produced by the interaction of the genotype and the environment'. The term "utilization of a metabolic nutrient" is also included, in the specification, page 13, as an example of phenotype. Since Applicants definition of phenotype encompasses other embodiments that would be not

be considered, 'the visible properties of an organism that are produced by the interaction of the genotype and the environment', it is not clear what phenotypes are considered "functions of the cell or tissue" so as to allow the metes and bounds of the claim to be determined.

Claim 24 is indefinite because it is not clear what is "utilization of a metabolic nutrient". Examiner interprets "utilization" to mean 'make use of' or 'turn to practical use or account'. It is not clear what is considered a metabolic nutrient, how the metabolic nutrient is made use of or turned to a practical use or account so as to allow the metes and bounds of the claim to be determined.

Claim 25 is indefinite because it is not clear whatparameter is determined when the phenotype of protein kinase catalytic activity is compared, as required in the base claim. What catalytic activity is measured? How is it measured? What method steps show the measurement of protein kinase catalytic activity?

Claim 26 is indefinite because it is not clear what is the natural binding a partner of C-RET so as to allow the metes and bounds of the claim to be determined. It is not clear what compounds are considered natural binding partners. It is also not clear when a binding partner is natural as compared to it not being natural. If a protein found in a particular cell line is introduced into another cell, which does not normally contain said protein, does the protein become not natural? If a compound is introduced into a cell line and it binds C-RET would it be considered a natural binding partner? The specification discloses the C-RET is an "orphan receptor" (page 16, lines 11-16). The specification further discloses, "It is called an orphan receptor because no ligand has

been identified which directly activates it" (page 16, 20-21). Since the specifcation does not disclose any ligands that bind C-RET it is not clear what is the natural binding partner so as to allow the metes and bounds of the claim to be determined. Further, the name natural binding partner is a functional term providing no structural information. Therefore it is not clear what compounds would be considered natural binding partners as compared to those that would be considered not natural binding partners so as to allow the metes and bounds of the claim to be determined.

Claim 27 is indefinite because it is not clear what is a phosphorylated product and how the protein kinase catalytic activity is measured so as to allow the metes and bounds of the claim to be determined. Further, the name phosphorylated product is a functional term providing no structural information. Therefore it is not clear what products could be phosphorylated by C-RET as compared to those that would be not phosphorylated by C-RET so as to allow the metes and bounds of the claim to be determined.

Claim 28 is indefinite because it is not clear what is the natural binding a partner of C-RET that is a protein comprising SH2 domains, a protein comprising SH3 domains, guanine nucleotide exchange factor, a protein phosphatase and protein kinase so as to allow the metes and bounds of the claim to be determined. The specification discloses the C-RET is an "orphan receptor" (page 16, lines 11-16). The specification further discloses, "It is called an orphan receptor because no ligand has been identified which directly activates it" (page 16, 20-21). Since the specifcation does not disclose any ligands that bind C-RET it is not clear what is the natural binding partner so as to allow

the metes and bounds of the claim to be determined. Also it is not clear what are SH2 domains, SH3 domains and guanine nucleotide exchange factor so as to allow the metes and bounds of the claim to be determined. What sequence of amino acids have to be present for a protein to be considered to have SH2 domains or SH3 domains. Further it is not clear what is the definition of guanine nucleotide exchange factor, SH2 domains or SH3 domains so as to allow the metes and bounds of the claim to be determined. Further, the name of the natural binding partner is a functional term providing no structural information. Therefore it is not clear what compounds would be considered natural binding partners as compared to those that would be considered not natural binding partners so as to allow the metes and bounds of the claim to be determined.

Claims 29 is rejected for depending upon an indefinite base (or intermediate) claim.

5. Claims 26, 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 26-28 are drawn the method of claim 23 wherein the phenotype is: a) the interaction between C-RET receptor protein and natural binding partner, or b) protein kinase catalytic activity measured by determining the rate or amount of phosphorylated product production by C-RET receptor protein.

The specification discloses the **C-RET is an "orphan receptor"** (page 16, lines 11-16). The specification further discloses, "It is called an orphan receptor because no ligand has been identified which directly activates it" (page 16, 20-21). The specification further states, "In addition, the **term "orphan receptor" as used herein refers to an RPTK without a known function"**, see page 16, lines 21-23. The specification clearly states that C-RET is an orphan receptor without a known function. Fox states discloses the functional ligand of RET receptor has not been identified (discussed above). The natural binding partner and protein kinase catalytic activity of phosphorylated product produced by C-RET receptor protein are not disclosed in the specification or prior art.

The claims, as written, encompass the use of compounds, which are natural binding partners of C-RET, and phosphorylated products produced by C-RET receptor protein, neither has been disclosed in the specification or prior art. Instant disclosure does not adequately describe the scope of the use of the claimed genus of said compounds. A description of a genus of claimed compounds for use in claimed method may be achieved by means of a recitation of a representative number of compounds, defined by specific structure, falling within the scope of the genus, or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of compounds. There is no description of the conserved

regions, which are critical to the structure, and function of the genus claimed. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to permit one of skill to isolate and identify the compounds encompassed. No identifying characteristic or property of the instant polypeptides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific polypeptide and nucleotide sequences and the inability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed. The skilled artisan cannot envision the detailed chemical structure of the encompassed compounds and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

The instant specification fails to provide sufficient descriptive information of the claimed compounds, such as definitive structural and functional features. **The common function of the claimed genus of compounds, which is based upon a structural common property or critical technical feature of the genus claimed is not disclosed.** Claims 26-28 are rejected for the reasons given above.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 23, 24, 25, 27-29 rejected under 35 U.S.C. 102(e) as being anticipated by Ibanez et al (US Patent 6,696,259).

Ibanez discloses a method of identifying one or more compounds (GDNF homologs) that modulate the function of C-RET receptor protein kinase, the method comprising expressing C-RET receptor protein in cells, contacting said cells with one or

more compounds, and comparing a phenotype of said cells to a phenotype of cells not expressing said C-RET receptor protein, or to a phenotype of cells expressing said C-RET receptor protein but not contacted with said compound (s), wherein a difference in said phenotypes identifies said compound(s) as modulator of C-RET function (see claim 1 and 2, Examples 1-26), therefore meeting the limitation of claim 23.

The compounds measured are homologs, defined as compound or composition having a similar biological effect as GDNF (column 10, lines 29-31), and inherently encompass any compound that would have an effect in claimed assay and therefore include peptide of less than 20 amino acids, a non-peptide organic molecule and an antibodies, absent evidence to the contrary. Drugs can also be tested for in claimed assay (column 15, lines 29-33)

Tyrosine phosphorylation of C-Ret disclosed in Fig 11; column 15, line 47-52.

Tyrosine phosphorylation and measurement of cell survival is disclosed on column 3, lines 5-15. The disclosure of tyrosine phosphorylation and cell survival meet the limitation of the phenotype cell survival of claim 24, protein kinase catalytic activity of claim 25.

Phosphorylation of ERKs is disclosed in Fig. 7. The disclosure of the phosphorylation of ERKs meets the limitation of the disclosing the phosphorylated product production by C-RET of claim 27.

Therefor the disclosure of Ibanez meets the limitation of claims 23, 24, 25, 27-29, absent evidence to the contrary.

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1646
June 24, 2004

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